

## Original Research Article

# A prospective study to evaluate the impact and independency of depth of invasion in comparison with other clinicopathologic prognostic variables in oral cavity malignancy

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## ABSTRACT

**Background:** Depth of invasion is included in the staging of oral cavity malignancies in the recent 8<sup>th</sup> edition of American Joint Committee on Cancer or tumour, node and metastasis staging system. This study analyses the impact of diffuse optical imaging (DOI) on incidence of lymph node involvement, stage migration, postoperative margin and independency.

**Methods:** Postoperative HPE of fifty patients with oral cavity malignancy operated in our institute from January 2018 were collected. Depth of invasion and other pathological parameters were documented. DOI divided into three groups and statistical analysis done.

**Results:** No lymph node metastasis is found in superficial tumours, 43% of intermediate thickness and 76% of deep tumours had lymph node involvement. Positive margin is seen only in patients with tumour DOI more than 0.5 cm, more than 50% of deep tumours had close margins while 75% of superficial tumours had adequate margin. Out of the 24 T3 tumours in this study 13 were upstaged due to inclusion of DOI, which would have been T2 according to the previous staging system. There is 54.1% (13 out of 24) upstaging in T3 tumours (T2 to T3), 23% (3 out of 13) in T2 (T1 to T2). There is no significant correlation between DOI and anatomical site, tumour size, tumour thickness, lymphovascular invasion and grade.

**Conclusions:** Depth of invasion in oral cavity malignancies impacts adversely lymph node metastasis and margin status. It is an independent prognostic factor in oral cavity malignancy.

**Keywords:** Depth of invasion, Close margin, Lymph node incidence, Oral cavity

## INTRODUCTION

Research, in the field of oncology has not only bettered the diagnostic and therapeutic fronts in cancer care but has also refined prognostication. Assigning a prognostic group is important in management of cancer patients as it helps to tailor appropriate treatment, balancing the morbidity and oncological outcomes.

Though depth of invasion of tumour, defined as the extent of tumour growth into the tissue beneath the

epithelial surface, is a long recognised prognostic variable in oral cavity malignancy especially in planning elective neck dissection, it was incorporated in the staging system only in the 8<sup>th</sup> edition of American Joint Committee on Cancer (AJCC) or tumour, node and metastasis (TNM) staging. Increasing T stage is assigned to sequential increase in depth of invasion. In contrast to tumour thickness measured from the apex of the tumour, depth of invasion is measured from the basement membrane to the farthest extent of the tumour.<sup>1</sup> Diffuse optical imaging (DOI) defines the invasiveness of the

tumour, differentiating the exophytic lesions from invasive lesions which form a distinct biological subset.<sup>1</sup> Hence DOI is an important prognostic variable not only in defining the extent of tumour spread and its stage but also in the overall behaviour and aggressiveness of the tumour.

The objective of this study was to compare the level of coherence of depth of invasion in oral cavity malignancy with other clinicopathologic variables in prognostication; to identify preoperative predictors of increasing depth of invasion; to define the significance of depth of invasion as an independent prognostic factor.

## METHODS

The prospective type of study was placed at Department of Surgical Oncology, Government Royapettah hospital during period of January to December 2018.

### Selection criteria

All oral cavity malignancy patients were operated.

The postoperative histopathology reports of fifty patients with oral cavity malignancy operated in the Surgical Oncology Department of Government Royapettah Hospital from January 2018 were collected. The values of the prognostic variables that would impact decision regarding adjuvant therapy were collected and grouped. All pathological parameters were reported by a single pathologist. Depth of invasion was measured by ocular micrometer. Tumour thickness and margins were measured during grossing of specimen. Lymph node involvement is expressed as a percentage of lymph nodes involved among the total lymph nodes examined by serial cut sections. The results were tabulated and analysis done by standard statistical methods using SPSS software.

## RESULTS

The collected data were grouped under three categories of DOI (less than 0.6 cm, 0.6 to 1 cm, more than 1 cm) as superficial, intermediate and deep in accordance with the AJCC staging manual and results were analysed.

Among the fifty patients in the study, most are carcinoma of tongue and buccal mucosa with an almost equal distribution, with less number from carcinoma alveolus, reflecting the incidence of the cancer in the population. Most of the superficial tumours (62.5%) are from tongue, with only 25% reported in buccal mucosa, among tongue cancers there is no statistically significant distribution among the three DOI groups, though there is a nonsignificant increase in intermediate and deep tumours among buccal mucosa cancers. In our analysis there is no statistically significant distribution of cancer among the three DOI groups in relation to the subsite of origin ( $p=0.720$ ).

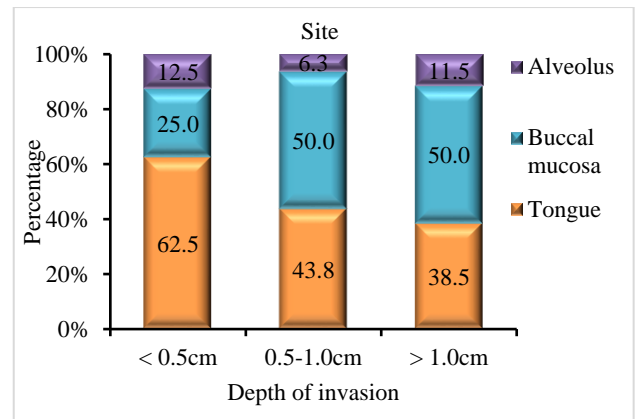


Figure 1: Subsite incidence.

In the analysis of tumour thickness among the DOI groups (Table 1), the mean tumour thickness in the superficial group is 0.725 cm, intermediate group is 1cm and deep group is 1.6 cm. There is no significant difference in tumour thickness between superficial and intermediate groups ( $p=0.432$ ), although in deep tumours the tumour thickness is significantly more ( $p=0.001$ ). Since there is no proportional increase in tumour thickness between the superficial and intermediate groups, it could be inferred that tumour thickness does not always signify invasiveness, and the depth of tumour invasion is independent of tumour thickness.

Table 1: Mean thickness.

Depth of invasion	N	Mean thickness	SD	f-value	P value
<0.5 cm	8	0.725	0.4803	10.219	<0.001
0.5-1.0 cm	16	1.006	0.3623		
>1.0 cm	26	1.692	0.7704		
<b>Total</b>	<b>50</b>	<b>1.318</b>	<b>0.7345</b>		

When the adequacy of margin status (Table 2) is analysed among the three groups, in the superficial tumour group 75% (6 out of 8) have adequate margin ( $>0.5$  cm). There is equal distribution of cases in adequate and close margin ( $<0.5$  cm) among the intermediate thickness group, whereas in deep tumours more than fifty percent of patients (13 out of 26) had close margins. Positive margin is seen only in patients with tumour DOI more than 0.5 cm. Thus, increasing tumour depth of invasion is associated with increasing risk of close margin.

Lymphovascular invasion is seen only in tumours more than 0.5 DOI, 18% in the intermediate and 19% in the deep group. Most of the tumours in this study had no LVSI, 100% in superficial group, 80% in the deep and intermediate group. There is no statistically significant distribution of tumours with regard to LVSI among the three groups (Table 3).

On analysis of tumour distribution among low grade and high grade (Table 4), its observed that both superficial

and deep tumours had more than 80% well differentiated carcinomas. There is a no significant distribution of

tumours in either grades among the three groups. No poorly differentiated tumours were in our study.

**Table 2: Margin status.**

Margin	Depth of invasion							
	<0.5 cm		0.5-1.0 cm		>1.0 cm		Total	
	N	%	N	%	N	%	N	%
Adequate	6	75.0	7	43.8	10	38.5	23	46.0
Positive	0	0	2	12.5	3	11.5	5	10.0
Close	2	25.0	7	43.8	13	50.0	22	44.0
Total	8	100.0	16	100.0	26	100.0	50	100.0

P value=0.5.

**Table 3: Lymphovascular and perineural invasion.**

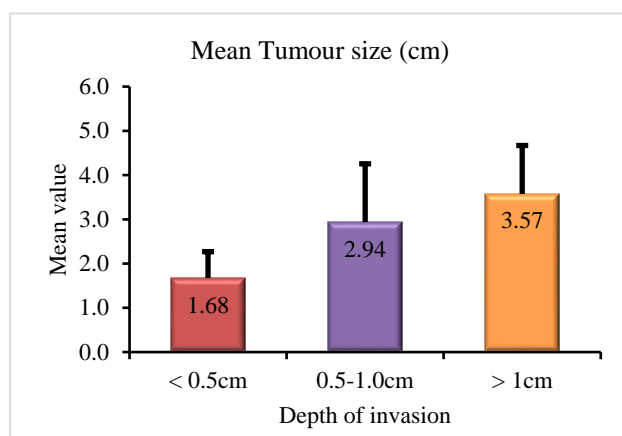
LVSI/PNI	Depth of invasion							
	<0.5 cm		0.5-1.0 cm		>1.0 cm		Total	
	N	%	N	%	N	%	N	%
No	8	100.0	13	81.3	21	80.8	42	84.0
Yes	0	0	3	18.8	5	19.2	8	16.0
Total	8	100.0	16	100.0	26	100.0	50	100.0

P=0.518.

**Table 4: Grade of tumour.**

Grade	Depth of invasion							
	<0.5 cm		0.5-1.0 cm		>1.0 cm		Total	
	N	%	N	%	N	%	N	%
Low grade	7	87.5	9	56.3	21	80.8	37	74.0
High grade	1	12.5	7	43.8	5	19.2	13	26.0
Total	8	100.0	16	100.0	26	100.0	50	100.0

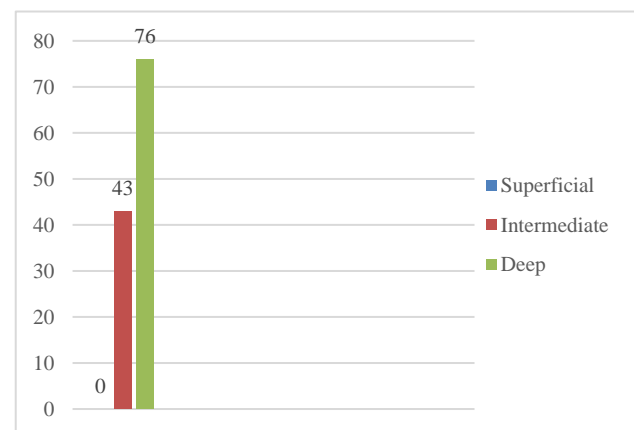
P=0.190.



**Figure 2: Tumour size.**

The mean tumour size in superficial tumours is 1.6 cm, in intermediate tumour is 2.9 cm and in deep tumours 3.5 cm. There is a statistically significant increase in tumour size between the superficial and intermediate ( $p<0.032$ ), and the superficial and deep group ( $p=0.001$ ). But there is no significant difference in tumour size between the intermediate and deep groups. It is inferred that though increase in size increased the depth of invasion, there is

no significant change in tumour size between the superficial and deep groups. Among small tumours <2 cm size there was no significant difference in distribution of tumour among the three groups, 42% (6 out of 11) are superficial tumours with intermediate and deep tumour distribution 27% (3 out of 11), 18% respectively. Thus, tumour size is not proportionately correlating with depth of invasion.



**Figure 3: Distribution of tumour.**

There is no lymph node metastasis found in superficial tumours, whereas 43% of intermediate thickness and 76% of deep tumours had lymph node involvement. There is statistically significant difference in the lymph node node involvement between each group ( $p=0.029$ ) between the intermediate and deep tumour group. Lymph node ratio is not significantly different between the intermediate and the deep tumour groups ( $p=0.45$ ).

The incorporation of depth of invasion in TNM staging has resulted in stage migration of tumour, out of the 24 T3 tumours in this study 13 were upstaged due to inclusion of DOI, which would have been T2 according to the previous staging system. There is 54.1% (13 of 24) upstaging in T3 tumours (T2 to T3), 23% (3 of 13) in T2 (T1 to T2).

## DISCUSSION

Decision making in the management of oral cavity malignancy is largely based on TNM staging, though the prognostic implications of increasing tumour thickness has been recognised since the 1980's from the work of Spiro et al, it is only in the 8th edition of AJCC depth of invasion is included in TNM staging system.<sup>2</sup> It was Moore et al who stated that tumour thickness and depth of invasion are not the same and a distinction has to be made.<sup>3</sup> While tumour thickness reflects the volume of the tumour, depth of invasion signifies the invasiveness and hence the biological behaviour of the tumour which alters the prognosis.<sup>1</sup> Though there are numerous studies evaluating the impact of DOI on lymphnode metastasis, margin status. This is one of the few pioneering studies to analyse the correlation of DOI of the tumour with various clinicopathologic prognostic factors and establish the impact and independency of DOI as a prognostic variable.

The cut off value of 4 mm DOI for elective neck dissection in oral cavity malignancy has been validated based on numerous early studies like byers et al.<sup>4</sup> In a recent study by Tarsitano et al to identify the cut-off value of infiltration depth for predicting the risk of lymph node metastasis of the neck in a well-defined population of surgically treated patients affected by stage T1 to T2 oral SCC of the tongue.<sup>5</sup> The mean infiltration depth of the N-negative group was found to be 2.4 mm which was substantially different from the mean value observed in the N-positive group at 5.5 mm. A meaningful cut-off was identified at an infiltration depth value of 4 mm. In coherence with the previous studies there is no lymph nodal metastasis in the superficial tumour group. There is a statistically significant increase in the incidence of lymph node metastasis between the intermediate and deep tumour groups (43 vs 76%), establishing that increasing depth of invasion has corresponding increase in the incidence of lymph node metastasis. This is attributed to increasing proximity to larger lymph and blood vessels located deep. Lymph node ratio is an established risk factor for recurrence and survival in oral

cavity malignancies.<sup>6</sup> In our study there was no difference in the lymph node ratio between the intermediate and deep tumour groups.

Postoperative margin status is an important predictor of local recurrence in oral cavity malignancy. Increasing depth of invasion is associated with closer margins. In a study by Payne et al on factors influencing status of margin in oral cavity malignancy it is stated that. Maximum tumour diameter and depth of invasion were significant factors relating to poorer margins ( $p=0.015$  and  $0.021$ ).<sup>7</sup> In our study more than 50% of deep tumours have close margins and more than 75% of superficial tumours have adequate margin thus signifying the importance of DOI in local tumour control.

Tumour thickness and maximum tumour size represent the tumour volume. In coherence with the postulates of Moore et al which states that depth of invasion is distinct from tumour thickness in our study there is no proportionate increase of depth of invasion and tumour size and thickness. It is inferred in our study that there is no significant change in tumour size between the superficial and deep groups. Depth of invasion reflects the invasive nature of the tumour and is a better and distinct prognostic variable when compared to tumour thickness and tumour size.

When using DOI as a T category modulator, in our study 54.1% of T3 tumours were upstaged from T2. In a study by Drivena et al of 135 patients with AJCC 7 T1 disease, 28 were upstaged to T2 (20.7%) and 9 to T3 (6.7%) in AJCC 8. For the 163 patients with T2 disease, 65 were upstaged to T3 (39.9%).<sup>8</sup> This is significant considering the role of adjuvant radiotherapy in T3 disease. Thus, the recent staging system has made more number of patients with oral carcinoma undergo multimodality management.

Higher grade is associated with increased risk of lymph node metastasis, lymphovascular invasion and perineural invasion is also associated with higher lymph node metastasis and closer margin as reported by Lawaetz et al.<sup>9</sup> In our study there was no correlation found between grade, LVSI and the depth of invasion. There is no statistically significant difference in DOI between the various subsites of oral cavity in this study.

The results of this study, though cannot be quantitatively generalised because of limited sample size it would be applicable for hypothesis. The impact of inclusion of DOI in the TNM staging on the disease free and overall survival of patients' needs further studies.

## CONCLUSION

Depth of invasion in oral cavity malignancies has profound impact on lymph node metastasis and margin status. It is distinct from tumour thickness and represents in invasive behaviour of the tumour. It is an independent prognostic factor in oral cavity malignancy.

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